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The evaluation of success and failure of methotrexate treatment in ectopic pregnancy

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ABSTRACT

Aim: Regardless of medical advancements, ectopic pregnancy (EP) is still an essential factor in the mortality rate of women of reproductive age. The main aim of this study was to determine predictive factors associated with the success of the response to treatment with single-dose and two-dose methotrexate (MTX) regimens in women with tubal EP.

Material and Method: This retrospective study examined the electronic records of 130 patients who underwent treatment due to EP were included in the study. The patients were divided into two groups: the successful MTX treatment group (n: 85) as the case group and the failure of MTX treatment group (n: 45) as the control group.

Results: Age-matched (30.62±4.36) and body mass index (BMI)-matched (24.37±2.29) patients diagnosed with EP were treated with MTX. The mean beta-human chorionic gonadotropin (β-hCG) value on the first day of treatment was 1639.84±524.96 mIU/mL in the successful and 5866.76±1875.51 mIU/mL in the unsuccessful group. 85 of 130 (65%) were successfully treated with MTX. Five of 45 (35%) failed medical treatment and required laparoscopic surgery. The longest ectopic mass diameter was significantly higher in the failure of MTX treatment group ($p<0.05$). There was a statistically significant difference between groups in regard to the β-hCG values on days 1, 4, 7, and 14. The β-hCG values on the first day were significantly higher in the failure of MTX treatment group($p <0.05$). There was no statistically significant difference between a single-dose regimen and multi-dose treatments.

Conclusion: We found that an initial β-hCG value was a predictive parameter for MTX's effective medical care of ectopic pregnancy. Vaginal bleeding was identified as a risk factor for the success of MTX treatment.

Keywords: Ectopic pregnancy, methotrexate, medical treatment

INTRODUCTION

Despite medical advances, ectopic pregnancy (EP) is still an important factor in the mortality rate of women of reproductive age (1-3). EP causes six percent of pregnant women's deaths in the first trimester of pregnancy, and only one-third of the women with EP with tubal rupture can give birth to a healthy child in the future (4-7). EP is referred to the implantation of fertilized oocytes in a place other than the endometrium. The most prevalent place is the fallopian tube (8). EP is a prevalent complication worldwide and its prevalence rate varies in different countries (9).

The EP prevalence in the west is about 2% among the general population, but it is as high as 20% among patients undergoing tubal surgery in a previous EP (10). No statistics have been published about the prevalence of EP among Turkish women. EP prevalence has been increasing in the last three decades (11).

EP is the main problem of women of reproductive age. It is usually manifested with symptoms of amenorrhea, lower abdominal pain, vaginal bleeding, mass in the uterine appendages, and some cases, rupture of the fallopian tube (12). EP occurs for different reasons, all of which prevent the successful migration of the fertilized oocytes to the endometrium (13). The most important risk factors for the occurrence of EP are tubal surgery even tubal ligation, history of the previous EP, fetal contact with diethylstilbestrol (DES) and history of pelvic inflammatory disease (PID) (14). Intrauterine devices (IUD) and infertility increase the chance of EP(15,16). It is challenging to diagnose EP due to extensive clinical manifestations (17). The known treatments for EP include surgery and pharmacotherapy using methotrexate (MTX) (18).

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Tanaka et al. (19) treated an interstitial pregnancy with MTX for the first time in 1982. MTX is a leucovorin antagonist that prevents DNA synthesis, cell repair and division by inhibiting the Dihydrofolate reductase enzyme, to which trophoblast tissue is highly sensitive. The common side effects of MTX include nausea, diarrhea, mouth ulcers, and liver disorders, and its rare side effects include neutropenia, fever, pneumonia, and alopecia. Hepatic complications are usually seen with high doses and are rarely seen after the dosage in EP (6). Single-dose and multiple-dose regimens are the two prevalent protocols for administering MTX (20).

This study investigated patients' success rates with single-dose and two-dose diets. Determining the predictive factors in the failure of this treatment is very important. This study aimed to identify factors predicting the success of the response to treatment using single and two-dose MTX regimens among the women who had tubal EP.

MATERIAL AND METHOD

This retrospective study was approved by the Bezmialem Foundation University Non-Interventional Clinical Researches Ethics Committee (Date: 06.09.2022, Decision No:2022/263) All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. One hundred nine women participated in this study form December 2019 -March 2022.

Women between the ages of 20 and 40 were included in this study. All women get pregnant spontaneously and with tubal. After performing the previously mentioned tests and measuring the body surface using weight and height, the patients were treated with MTX, 50mg/m2 intramuscularly, MTX injection day was considered as day one. Then, beta human chorionic gonadotropin (β-hCG) was measured again in the same center on days four, seven and fourteen. If this reduction was below 15% between days four and seven, the second dose of MTX started with the same initial dose of the injection and started again with a new day. In case of a heartbeat after injection doses, intra-abdominal bleeding, or severe pain along with the unstable hemodynamic status of the patient, laparotomy was performed.

In this study, successful treatment was considered as the complete return of β-hCG level to below 10 mIU/ml after the initial dose of MTX without any other internal or surgical intervention. Patients who needed more than one dose or underwent surgery had treatment failure. In the end, the patients of the successful group (n=85) were compared with those of the failure group (n=45) in terms of factors predicting this success rate.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to check the normality, and the nonparametric tests were performed given the non-normality of the groups before the statistical analyses. Mean and standard deviations (SD) were measured to check each continuous variable, including age, body mass index (BMI), hemoglobin (Hb), platelet (PLT), Aspartate Aminotransferase (AST), Alanine Aminotransferease (ALT), blood urea nitrogen (BUN), β-hCG. The Mann-Whitney U test was performed to study the difference between the two groups. SPSS v22 was used for statistical analyses. A value of $p < 0.05$ was accepted as statistically significant.

To calculate the sample size with the G-Power 3.1 program, the two groups' total mean was measured based on the Mann-Whitney test with a power of 95%, effect size of 50%, and 0.05 type 1 error for at least 92 patients (21).

RESULTS

This study included one hundred thirty women age-matched (30.62±4.36) and BMI-matched (24.37±2.29). The descriptive statistics of study parameters were omitted for brevity.

As stated in **Table 1**, a Mann-Whitney test did not find a statistically significant association between case and control in regard to age and BMI ($p>0.05$). Kruskal–Wallis H did not find a statistically significant association between groups in regard to age, BMI, PLT, AST, ALT, and BUN ($p>0.05$). There was a significant difference between the three groups in terms of the β-hCG values on days 1, 4, 7, and 14 ($p<0.05$) (**Table 2**). The Hb was significantly lower in the unsuccessful group ($p<0.05$). The longest ectopic mass diameter was significantly higher in the unsuccessful group ($p<0.05$).

As stated in **Table 2**, Mann-Whitney U did not find a statistically significant association between successful MTX treatment and failed MTX treatment regarding age, BMI, PLT, AST, ALT, and BUN ($p>0.05$). The β-hCG values on the first day were significantly higher in the unsuccessful group compared successful group (1639–5866) ($p<0.05$). The β-hCG values on days 4, 7, and 14 were significantly lower in the unsuccessful group compared successful group (1639–5866, 1517–796, 1099–81, and 35–7) ($p<0.05$). The Hb was significantly lower in the unsuccessful group ($p<0.05$). The longest ectopic mass diameter was significantly higher in the unsuccessful group ($p<0.05$).

Table 1. Comparison of numeric parameters between three groups

Study parameters	Successful MTX after first doses M±SD (n=47)	Successful MTX after second doses M±SD (n=38)	Failure of MTX treatment M±SD (n=45)	p
Age	30.6±4.04	30.63±5.07	30.64±4.14	0.998*
BMI	24.06±1.8	24.66±2.76	24.45±2.33	0.216**
Hb	11.26±0.82	11.4±0.69	7.97±0.69	**<0.001****
PLT	253893.62±61685.82	247184.21±67119.44	271711.11±66705.13	0.202*
AST	15.74±9.31	13.32±3.73	14.53±3.15	0.088**
ALT	16.85±5.56	17.37±7.51	15.69±4.21	0.710**
BUN	17.85±5.13	17.68±5.24	17.98±4.46	0.893**
D-0 β-hCG	1362.43±231.64	1982.95±583.34	5866.76±1875.51	**<0.001****
D-4 β-hCG	1018.79±266.94	2133.37±664.51	796±343.68	**<0.001****
D-7 β-hCG	828.68±251.47	1433.68±457.62	81.69±41.63	**<0.001****
D-14 β-hCG	18.72±12.11	56.66±50.12	7.98±6.55	**<0.001****
Longest ectopic mass diameter (mm)	12.3±3.95	30.84±4.74	44.29±6.94	**<0.001***

M, Mean; N, number of subjects; SD, standard deviation; MTX, methotrexate; BMI, body mass index; Hb, hemoglobin; PLT, platelet; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferease; BUN, blood urea nitrogen; β-hCG, Beta human chorionic gonadotropin. *One way ANOVA; **Kruskal–Wallis H test

Table 2. Comparison of numeric parameters between two groups

Study parameters	Successful MTX treatment (first or second doses) M±SD (n=85)	Failure of MTX treatment M±SD (n=45)	p
Age	30.61±4.5	30.64±4.14	0.982
BMI	24.33±2.28	24.45±2.33	0.467
Hb	11.32±0.76	7.97±0.69	**<0.001**
PLT	250894.12±63870.04	271711.11±66705.13	0.176
AST	14.66±7.42	14.53±3.15	0.062
ALT	17.08±6.47	15.69±4.21	0.475
BUN	17.78±5.15	17.98±4.46	0.636
D-0 β-hCG	1639.84±524.96	5866.76±1875.51	**<0.001**
D-4 β-hCG	1517.07±737.75	796±343.68	**<0.001**
D-7 β-hCG	1099.15±467.36	81.69±41.63	**<0.001**
D-14 β-hCG	35.68±39.33	7.98±6.55	**<0.001**
Longest ectopic mass diameter (mm)	20.59±10.22	44.29±6.94	**<0.001**

M, Mean; N, number of subjects; All variables tested by a Mann-Whitney U test.

Table 3 shows the comparison of nominal parameters in three groups. As can be seen, the highest frequency of localization information in total was tubal (93.1%), ovarian (2.3%), cervical (2.3%), cesarean scar (2.3%), and abdominal (0%). There was not a statistically significant association between demographic features (smoking, gravida and abortus) and MTX treatment results (p> 0.05). There was not a statistically significant association between localization information and MTX treatment results (p> 0.05). There was a statistically significant association between parity and MTX treatment results (p> 0.05).

As stated in **Table 4**, there was not a statistically significant association between demographic features(localization, smoking, gravida, abortus, and parity) and MTX treatment results (p> 0.05).

Table 5 compares presenting symptoms and historical factors in three groups. As can be seen, there was not a statistically significant association between historical factors (abortion, infertility, insemination,in vitro fertilization, PID, endometriosis, pelvic surgery, and EP) and MTX treatment results (p> 0.05). There was a statistically significant association between vaginal bleeding as presenting symptoms and MTX treatment results (p-value < 0.05). The Pairwise Z-Tests found that the vaginal bleeding was significantly higher in the unsuccessful group.

There was a statistically significant association between pain as presenting symptoms and MTX treatment results (p< 0.05). The Pairwise Z-Tests found that the pain was significantly higher than in the successful group.

Table 3. Comparison of demographic features between three groups

Study parameters	Categories	Total	Successful MTX after first doses (n=47) n(%)	Successful MTX after second doses (n=38) n(%)	Failure of MTX treatment (n=45) n(%)	p
Localization						1*
	Tubal	121 (93.1)	44 (93.6)	35 (92.1)	42 (93.3)	
	Ovarian	3 (2.3)	1 (2.1)	1 (2.6)	1 (2.2)	
	Cervical	3 (2.3)	1 (2.1)	1 (2.6)	1 (2.2)	
	Cesarean Scar	3 (2.3)	1 (2.1)	1 (2.6)	1 (2.2)	
	Abdominal	0 (0)	0 (0)	0 (0)	0 (0)	
Smoking						0.247*
	No	59 (45.4)	23 (48.9)	20 (52.6)	16 (35.6)	
	Yes	71 (54.6)	24 (51.1)	18 (47.4)	29 (64.4)	
Gravida						0.115*
	1	67 (51.5)	27 (57.4)	18 (47.4)	22 (48.9)	
	2	54 (41.5)	17 (36.2)	20 (52.6)	17 (37.8)	
	3	9 (6.9)	3 (6.4)	0 (0.0)	6 (13.3)	
Abortus						0.541*
	0	105 (80.8)	35 (74.5)	32 (84.2)	38 (84.4)	
	1	24 (18.5)	11 (23.4)	6 (15.8)	7 (15.6)	
	2	1 (0.8)	1 (2.1)	0 (0.0)	0 (0.0)	
Parity						**0.010***
	No	83 (63.8)	38 (80.9)	21 (55.3)	24 (53.3)	
	Yes	47 (36.2)	9 (19.1)	17 (44.7)	21 (46.7)	

*Pearson Chi-Square Test † The Pairwise Z-Tests

Table 4. Comparison of demographic features between two groups

Study parameters	Categories	Total	Successful MTX treatment (n=85) n(%)	Failure of MTX treatment (n=45) n(%)	p
Localization					1*
	Tubal	121 (93.1)	79 (92.9)	42 (93.3)	
	Ovarian	3 (2.3)	2 (2.4)	1 (2.2)	
	Cervical	3 (2.3)	2 (2.4)	1 (2.2)	
	Cesarean Scar	3 (2.3)	2 (2.4)	1 (2.2)	
	Abdominal	0 (0)	0 (0)	0 (0)	
Smoking					0.101*
	Yes	59 (45.4)	43 (50.6)	16 (35.6)	
	No	71 (54.6)	42 (49.4)	29 (64.4)	
Gravida					0.110*
	1	67 (51.5)	45 (52.9)	22 (48.9)	
	2	54 (41.5)	37 (43.5)	17 (37.8)	
	3	9 (6.9)	3 (3.5)	6 (13.3)	
Abortus					0.619*
	0	105 (80.8)	67 (78.8)	38 (84.4)	
	1	24 (18.5)	17 (20.0)	7 (15.6)	
	2	1 (0.8)	1 (1.2)	0 (0.0)	
Parity					0.069*
	Yes	83 (63.8)	59 (69.4)	24 (53.3)	
	No	47 (36.2)	26 (30.6)	21 (46.7)	

*Pearson Chi-Square Test

Table 5. The presenting symptoms and historical factors of three groups

Presenting symptoms and historical factors of three groups	Total	Successful MTX treatment n (%)	Successful MTX 2 Doses treatment n (%)	Failure of MTX treatment n (%)	p
Vaginal Bleeding	97 (51)	27 (35)	30 (56.6)	40 (66.7)†	**0.002***
Pain	48 (25)	26 (34)†	15 (28.3)†	7 (11.7)	**<0.001***
Abortion Story	5 (3)	3 (4)	1 (1.9)	1 (1.7)	0.525*
Infertility History	10 (5)	5 (6)	2 (3.7)	3 (5)	0.620*
Insemination History	9 (5)	6 (8)	1 (1.9)	2 (3.3)	0.135*
In vitro fertilization	10 (5)	4 (5)	1 (1.9)	5 (8.3)	0.340*
Pelvic Inflammatory Disease History	3 (2)	1 (1)	1 (1.9)	1 (1.7)	0.987*
Endometriosis History	2 (1)	1 (1)	0 (0)	1 (1.7)	0.657*
Pelvic Surgery History	2 (1)	1 (1)	1 (1.9)	0 (0)	0.574*
Ectopic Pregnancy History	4 (2)	3 (4)	1 (1.9)	0 (0)	0.209*

*Pearson Chi-Square Test † The Pairwise Z-Tests

DISCUSSION

The most prominent finding of this research was the significant relationship between patients' symptoms and the success of MTX treatment. Women with symptoms of vaginal bleeding significantly responded negatively to MTX treatment and became candidates for surgery. Pain symptoms in patients who respond positively to MTX treatment are prevalent. This study reports that 34.6% of patients needed surgical excision. Existing literature shows surgical intervention is necessary in 5–25% of cases (22-25).

This study showed no statistically significant difference between a single-dose regimen and multi-dose treatments. According to previous studies, there is an association between a single-dose regimen and a higher failure rate than a multi-dose regimen (12% vs. 7%) (26). On the contrary, equal significance between the two protocols was reported in some studies (27). Since the single-dose method is associated with side effects and lower costs, it is more accepted. One of its disadvantages is that a percentage of patients do not respond sufficiently to the initial dose, increasing the need for more doses, or they may suffer from severe abdominal pain and rupture of the pregnancy site during the treatment, resulting in surgery and treatment failure. Knowing the predictive factors of treatment failure to prevent these cases is essential.

Although it has been known that high levels of pretreatment β-hCG are the most important predicting factor related to MTX treatment failure, it remains unclear which treatment modality is suitable for a specific range of pretreatment β-hCG values (22, 28). Lipscomb et al. (29) reported that the initial β-hCG value is the most important factor determining failure in single-dose regimen of MTX treatment. Mol et al. (18) compared the impact of β-hCG values on single-dose regimens ad multi-dose regimens of MTX treatment. When the β-hCG value is less than 1500mIU/ml, the single-dose regimen is recommended, and the multi-dose regimen should be used when it is less than 3000mIU/ml. Erdem et al. (20) demonstrated that the β-hCG value above 4000mIU/ml is the most important cause of MTX treatment failure. Menon et al. (30) patients with the β-hCG value above 5000mIU/ml are more likely to fail MTX treatment. Our study confirms these results. The β-hCG value is a determining factor in the success of the treatment. In our study, according to the mean level of the β-hCG value on the first day (5866mIU/ml), the β-hCG value above 5000mIU/ml is a significant risk factor in treatment failure.

The limitations of a study are the small sample size and single center. For this cause, more interventional and observational trials should be done based on a more complete multiple-center randomized. For future work, we will design a survey study on women with vaginal bleeding and pain symptoms regarding MTX treatment.

CONCLUSION

As a result, we demonstrated that initial β-hCG values were predictive parameters for the effective medical treatment of EP by MTX. An initial β-hCG value>5000 mIU/ml was predictive of its failure. Vaginal bleeding was identified as a predictive factor of MTX treatment failure. There were no significant differences between single-dose and multi-dose MTX protocols in terms of the successful treatment of EP

ETHICAL DECLARATIONS

Ethics Committee Approval: This retrospective study was approved by the Bezmialem Foundation University Non-Interventional Clinical Researches Ethics Committee (Date: 06.09.2022 Decision No:2022/263).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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